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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/781,133	02/09/2001	Neil J. Hayward	PPI-064	1688

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EXAMINER
RUSSEL, JEFFREY E

ART UNIT	PAPER NUMBER
1654	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/781,133	Applicant(s) HAYWARD ET AL.	
	Examiner Jeffrey E. Russel	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. Claim 24 is objected to because of the following informalities: At claim 24, line 4, "polypeptide" should be changed to "peptide" so that claim terminology is consistent. Appropriate correction is required.

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 24-32 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6, 7, and 15-17 of copending Application No. 09/519,019 in view of the WO Patent Application 98/08868, Kroin et al (U.S. Patent No. 5,776,939), and the WO Patent Application 95/20980. The '019 application claims the PPI-1019 β-amyloid peptide derivative and pharmaceutical compositions for delivering PPI-1019 across the blood-brain barrier. However, the '019 application does not claim a method for administering PPI-1019 across the blood-brain barrier, does not claim oral administration of the PPI-1019, and does not claim co-administration of a P-glycoprotein inhibitor or a cytochrome P450 inhibitor in order to improve the oral administration or in order to increase the crossing of the blood-brain barrier. The WO Patent Application '868 teaches β-amyloid peptide derivatives which are structurally and functionally analogous to the PPI-1019 β-amyloid peptide derivative claimed by the '019 application (see, e.g., the Abstract and the

claims), and teaches the desirability of oral administration of the β-amyloid peptide derivatives (see, e.g., page 33, lines 7-8) and discloses the desirability of administration of the β-amyloid peptide derivatives so that they cross the blood-brain barrier (see, e.g., page 34, line 34 - page 35, line 5). Kroin et al teach co-administration of drugs with a compound of Formula (C) so that the oral bioavailability of the drugs and the bioavailability of the drugs to the brain is enhanced. The compounds of Formula (C) are P-glycoprotein inhibitors. The drugs and the compounds of Formula (C) are administered simultaneously or at different times. See, e.g., column 2, lines 53-60; column 4, lines 4-17; column 9, lines 39-42; column 25, lines 57-64; and column 26, lines 4-6. The WO Patent Application '980 teaches co-administration of an orally administered drug with an inhibitor of a cytochrome P450 3A enzyme and/or an inhibitor of P-glycoprotein-mediated membrane transport so that the bioavailability of the drug is increased. Cyclosporine, SDZ PSC-833 (i.e. valspodar), antiarrhythmics, antibiotics, antifungals, antiparasites, calcium channel blockers, cancer chemotherapeutics, hormones, local anesthetics, phenothiazines, and tricyclic antidepressants are disclosed as useful inhibitors. The drugs and inhibitors can be administered simultaneously or at different times. See, e.g., the Abstract; page 12, lines 9-17; page 13, line 22 - page 14, line 8; page 18; page 26; and page 32, line 30 - page 33, line 5. It would have been obvious to one of ordinary skill in the art to administer the claimed compound of the '019 application by the same methods disclosed by the WO Patent Application '868 for its β-amyloid peptide derivatives because it is routine in the art to administer a drug by the same methods and for the same purposes as other prior art analogs of the drug have been administered, and because it is prima facie obvious to use a product consistently with the intended use limitation recited in a claim drawn to the product (see claim 17 of the '019 application). It would

have been obvious to one of ordinary skill in the art to co-administer the PPI-1019 β-amyloid peptide derivative claimed by the '019 application with the P-glycoprotein inhibitors and/or the cytochrome P450 inhibitors of Kroin et al or the WO Patent Application '980 because the methods of Kroin et al and the WO Patent Application '080 are disclosed to be useful for a wide variety of drugs, and because the methods of Kroin et al and the WO Patent Application '080 would have been expected to be useful in aiding and increasing the oral administration and the crossing of the blood-brain barrier which are suggested to be desirable for PPI-1019 by the WO Patent Application '868.

This is a provisional obviousness-type double patenting rejection.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 24, 25, 31, and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 98/08868 in view of Applicants' admission at page 11, lines 2-3, of the specification. The WO Patent Application '868 teaches β-amyloid peptide derivatives which are administered in vivo to the CNS or across the BBB for the diagnosis and treatment of amyloidogenic diseases. Administration can be as a single bolus or a several divided doses. Supplementary active compounds can be incorporated into the compositions. Two or more of the β-amyloid peptide derivatives may be used in combination. Particularly exemplified β-amyloid peptide derivatives include PPI-558, PPI-578, PPI-655, and PI-657. See, e.g., page 5, lines 26-32; page 32, lines 22-25; page 33, lines 13-14; page 36, lines 31-32; page 39, line 32 - page 41, line 8; and Tables VIII, X, and XI. With respect to the teachings in the WO Patent Application '868 of the administration of two or more β-amyloid peptide derivatives in

combination, again Applicants admit at page 11, lines 2-3, that β-amyloid peptide derivatives are themselves P-glycoprotein inhibitors. Accordingly, at least one of the β-amyloid peptide derivatives in the WO Patent Application '868's combination can be designated as corresponding to Applicants' β-amyloid peptide derivative, and at least one of the other β-amyloid peptide derivatives in the WO Patent Application '868's combination can be designated as inherently corresponding to Applicants' P-glycoprotein inhibitor.

5. Claims 24, 25, and 27-32 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 98/08868 as applied against claims 24, 25, 31, and 32 above, and further in view of Kroin et al (U.S. Patent No. 5,776,939) or the WO Patent Application 95/20980. The WO Patent Application '868 discloses the desirability of oral administration of the β-amyloid peptide derivatives (see, e.g., page 33, lines 7-8) and discloses the desirability of administration of the β-amyloid peptide derivatives so that they cross the blood-brain barrier (see, e.g., page 34, line 34 - page 35, line 5), but does not recite co-administration of a P-glycoprotein inhibitor or a cytochrome P450 inhibitor in order to improve the oral administration or in order to increase the crossing of the blood-brain barrier. Kroin et al teach co-administration of drugs with a compound of Formula (C) so that the oral bioavailability of the drugs and the bioavailability of the drugs to the brain is enhanced. The compounds of Formula (C) are P-glycoprotein inhibitors. The drugs and the compounds of Formula (C) are administered simultaneously or at different times. See, e.g., column 2, lines 53-60; column 4, lines 4-17; column 9, lines 39-42; column 25, lines 57-64; and column 26, lines 4-6. The WO Patent Application '980 teaches co-administration of an orally administered drug with an inhibitor of a cytochrome P450 3A enzyme and/or an inhibitor of P-glycoprotein-mediated membrane transport so that the bioavailability of

the drug is increased. Cyclosporine, SDZ PSC-833 (i.e. valspodar), antiarrhythmics, antibiotics, antifungals, antiparasites, calcium channel blockers, cancer chemotherapeutics, hormones, local anesthetics, phenothiazines, and tricyclic antidepressants are disclosed as useful inhibitors. The drugs and inhibitors can be administered simultaneously or at different times. See, e.g., the Abstract; page 12, lines 9-17; page 13, line 22 - page 14, line 8; page 18; page 26; and page 32, line 30 - page 33, line 5. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to co-administer the β-amyloid peptide derivatives of the WO Patent Application '868 with the P-glycoprotein inhibitors and/or the cytochrome P450 inhibitors of Kroin et al or the WO Patent Application '980 because the methods of Kroin et al and the WO Patent Application '080 are disclosed to be useful for a wide variety of drugs, and because the methods of Kroin et al and the WO Patent Application '080 would have been expected to be useful in aiding and increasing the oral administration and the crossing of the blood-brain barrier taught desirable by the WO Patent Application '868.

6. Applicant's arguments filed March 12, 2003 have been fully considered but they are not persuasive.

Applicants' attorney's statement of common ownership at the time the invention was made satisfies the requirement set forth in paragraph 6 of the previous Office action and overcomes the provisional obviousness rejection set forth in paragraph 9 of the previous Office action. It should be noted that there was no provisional rejection of the claims under 35 U.S.C. 102(e) over Application No. 09/519,019 in the previous Office action.

The anticipation rejection over the WO Patent Application 98/08868 in view of Applicants' admission at page 11, lines 2-3, of the specification is maintained with respect to the

WO Patent Application '868's teaching of the use of two or more β-amyloid peptide derivatives in combination. Applicants' response did not address this aspect of the rejection.

The anticipation rejection of claims 24 and 31 over the WO Patent Application 98/08868 in view of the WO Patent Application 95/20980 set forth in paragraph 11 of the previous Office action is withdrawn in view of the amendments to the independent claim.

The obviousness rejection based upon the WO Patent Application 98/08868 in view of Kroin et al (U.S. Patent No. 5,776,939) or the WO Patent Application 95/20980 is maintained. Motivation for the combination of the references is established by the references and is explained in the rejection. The examiner agrees with Applicants' summary of the case law as set forth in the response, but believes that the obviousness rejection is consistent with the cite case law. In particular, it is not the examiner but rather it is the WO Patent Application '868 that discloses oral administration and that discloses administration so that the β-amyloid peptide derivatives cross the blood-brain barrier. It should be noted that the disclosure of a reference is not limited to the reference's most preferred embodiments, and that the preferred embodiment of a reference does not teach away from the reference's disclosed non-preferred embodiments. See MPEP 2123. It is not the examiner but rather it is Kroin et al and the WO Patent Application '980 which teach co-administration of drugs with certain compounds so that the oral administered drug crosses the blood-brain barrier. The combination of the goal disclosed in the WO Patent Application '868 with a prior art solution to that goal as disclosed in Kroin et al or the WO Patent Application '980 is prima facie obvious. It is not relevant that the WO Patent Application '868 may disclose a plethora of ways for achieving its disclosed results or that the WO Patent Application '868 by itself does not suggest Applicants' claimed invention. It is permissible to

combine references under 35 U.S.C. 103, and it is the prior art as a whole, i.e. the combination of references rather than the individual references, which must be considered in determining the obviousness of Applicants' claimed invention.

Figures 4 and 6 and their accompanying description in the specification have been carefully considered, but are not deemed to establish unexpected results which would rebut any prima facie case of anticipation. In particular, the Figures are not commensurate in scope with the claims, e.g., do not test a representative number of β-amyloid peptide derivatives and do not test a representative number of P-glycoprotein inhibitors. Further, the description of the experimental details which resulted in Figure 6 (see page 48, lines 19-25, of the specification) is insufficient to establish that a side-by-side probative comparison was made between administration in the presence of and in the absence of a p-glycoprotein inhibitor. More experimental details, e.g., of the animals test, how the drugs were administered, and at what dosages, is required. In the absence of such experimental details, it is not possible to conclude that it is the use of a p-glycoprotein inhibitor, rather than some other experimental detail, which resulted in the significantly reduced liver accumulation illustrated in Figure 6.

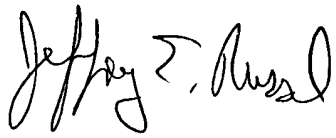
7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Art Unit 1654 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

April 23, 2003